AMENDMENT OF SOLICITATION/MODIFICATION OF CONTRACT

1. CONTRACT ID CODE	PAGE	OF	PAGES
	1		7

2. AMENDMENT/MODIFICATION NO.	3. EFFECTIVE DATE	4. REQUISITION/PURCHASE REQ. NO.	5. PROJECT NO. *(If applicable)*
0001	10/24/2013		

6. ISSUED BY CODE

National Cancer Institute
Office of Acquisitions
9609 Medical Center Drive, 1E564, MSC 9700
Bethesda, MD 20892-9700

7. ADMINISTERED BY *(If other than Item 6)* CODE

8. NAME AND ADDRESS OF CONTRACTOR *(No., street, county, State and ZIP Code)*

TO ALL POTENTIAL OFFERORS

CODE FACILITY CODE

(X) 9A. AMENDMENT OF SOLICITATION NO.

[X] PHS 2014-1

9B. DATED *(SEE ITEM 11)*

08/29/2013

10A. MODIFICATION OF CONTRACT/ORDER NO.

[ ]

10B. DATED *(SEE ITEM 13)*

11. THIS ITEM ONLY APPLIES TO AMENDMENTS OF SOLICITATIONS

[X] The above numbered solicitation is amended as set forth in Item 14. The hour and date specified for receipt of Offers [X] is extended, [ ] is not extended.

Offers must acknowledge receipt of this amendment prior to the hour and date specified in the solicitation or as amended, by one of the following methods: (a) By completing items 8 and 15, and returning 1 copies of the amendment; (b) By acknowledging receipt of this amendment on each copy of the offer submitted; or (c) By separate letter or telegram which includes a reference to the solicitation and amendment numbers. FAILURE OF YOUR ACKNOWLEDGMENT TO BE RECEIVED AT THE PLACE DESIGNATED FOR THE RECEIPT OF OFFERS PRIOR TO THE HOUR AND DATE SPECIFIED MAY RESULT IN REJECTION OF YOUR OFFER. If by virtue of this amendment your desire to change an offer already submitted, such change may be made by telegram or letter, provided each telegram or letter makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.

12. ACCOUNTING AND APPROPRIATION DATA *(If required)*

13. THIS ITEM ONLY APPLIES TO MODIFICATION OF CONTRACTS/ORDERS. IT MODIFIES THE CONTRACT/ORDER NO. AS DESCRIBED IN ITEM 14.

CHECK ONE	
[ ]	A. THIS CHANGE ORDER IS ISSUED PURSUANT TO: *(Specify authority)* THE CHANGES SET FORTH IN ITEM 14 ARE MADE IN THE CONTRACT ORDER NO. IN ITEM 10A.
[ ]	B. THE ABOVE NUMBERED CONTRACT/ORDER IS MODIFIED TO REFLECT THE ADMINISTRATIVE CHANGES *(such as changes in paying office, appropriation date, etc.)* SET FORTH IN ITEM 14, PURSUANT TO THE AUTHORITY OF FAR 43.103(b).
[ ]	C. THIS SUPPLEMENTAL AGREEMENT IS ENTERED INTO PURSUANT TO AUTHORITY OF:
[ ]	D. OTHER *(Specify type of modification and authority)*

E. IMPORTANT: Contractor [ ] is not, [ ] is required to sign this document and return _____ copies to the issuing office.

14. DESCRIPTION OF AMENDMENT/MODIFICATION *(Organized by UCF section headings, including solicitation/contract subject matter where feasible.)*

The purpose of this amendment is to: Extend the proposal due date to November 25, 2013, 4:30PM Eastern Time, revise SECTION 6.3 FAST TRACK (NIH ONLY)/Phase II Technical Evaluation Criteria and SECTION 12 COMPONENT INSTRUCTIONS AND TOPIC DESCRIPTIONS for NATIONAL INSTITUES OF HEALTH, TOPIC 332 FOR THE NATIONAL CANCER INSTITUTE AND TOPIC 027 FOR THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES.

See Page 2

Except as provided herein, all terms and conditions of the document referenced in Item 9A or 10A, as heretofore changed, remains unchanged and in full force and effect.

15A. NAME AND TITLE OF SIGNER *(Type or print)*		16A. NAME AND TITLE OF CONTRACTING OFFICER *(Type or print)*	
		Elizabeth J. Shanahan	
15B. CONTRACTOR/OFFEROR	15C. DATE SIGNED	16B. UNITED STATES OF AMERICA	16C. DATE SIGNED
(Signature of person authorized to sign)		*(Signature of Contracting Officer)*	10/24/2013

Accordingly, the closing date and the deadline for receipt of proposals is revised from **November 13, 2013, 4:30PM Eastern time to November 25, 2013, 4:30PM Eastern Time.**

SECTION 6.3 FAST TRACK (NIH ONLY)/Phase II Technical Evaluation Criteria is revised and replaced as follows:

6.3 FAST TRACK (NIH ONLY)/Phase II Technical Evaluation Criteria

FACTORS FOR PHASE II PROPOSALS	WEIGHT
1. The soundness and technical merit of the proposed approach based on: a. Identification of clear measureable goals (milestones) that have a reasonable chance of meeting the topic objective in Phase II; b. The approach is innovative and not routine, c. Offeror's ability to implement technical approach, i.e., has or can obtain the resources (facilities, personnel and equipment) suitable to the task.	30%
2. The potential of the proposed research for commercialization, as documented in the offeror's Commercialization Plan and evidenced by (a) the offeror's record of successfully commercializing its prior SBIR/STTR or other research projects (b) commitments of additional investment during Phase I and Phase III from private sector or other non-SBIR funding sources, and (c) any other indicators of commercial potential for the proposed research.	30%
3. The qualifications of the proposed PDs/PIs, supporting staff and consultants. For proposals designating multiple PDs/PIs, is the leadership approach, including the designated roles and responsibilities, governance, and organizational structure, consistent with and justified by the aims of the project and the expertise of each of the PDs/PIs?	25%
4. The adequacy and suitability of the facilities and research environment.	15%

Technical reviewers will base their conclusions only on information contained in the proposal. It cannot be assumed that reviewers are acquainted with the firm or key individuals or any referenced experiments. Relevant supporting data such as journal articles, literature, including Government publications, etc., should be contained or referenced in the proposal and will count toward the page limit.

Section 12 COMPONENT INSTRUCTIONS AND TECHNICAL TOPIC DESCRIPTIONS, NATIONAL INSTITUTES OF HEALTH, NATIONAL CANCER INSTITUTE, Topic 332 is revised and replaced in its entirety as follows:

Topic 332 Development of Radiation Modulators for Use During Radiotherapy

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 3 – 5

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,500,000 for 2 years.

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded

Summary

Radiotherapy is employed in the treatment of over half of all cancer patients. Many of those patients, however, may suffer some adverse effects from this therapy during and/or after treatment. In addition, in approximately half of the patients treated with curative intent, the tumors recur. Enhancing specific tumor killing and minimizing normal tissue damage from radiotherapy would improve tumor control and patient quality of life.

Radiosensitizers are agents that are intended to enhance tumor cell killing while having a minimal effect on normal tissues. Recently, two new radiation sensitization drugs have proven clinically effective: Temozolomide treatment with radiotherapy for glioblastoma and Cetuximab treatment combined with radiation for head and neck squamous cell cancers. A large number of other targeted therapies are possible and although some are currently in varying phases of development, there is significant potential for further development of novel agents. Examples of such targeted molecular therapies include radiation effect enhancers of reactive oxygen species (ROS), DNA damage response modifiers, as well as agents that alter chromatin organization, cellular responses, and tumor microenvironment (1). Any agent that acts via multiple mechanisms of action or combinations of agents that act via complementary mechanisms of action may also improve therapeutic gain.

Conventionally, *radioprotectors* are defined as agents given before radiation exposure to prevent or reduce damage to normal tissues, while *mitigators* refer to those agents given during or after a patient's prescribed course of radiation therapy to prevent or reduce imminent damage to normal tissues. Both radioprotectors and mitigators are also being developed as potential countermeasures against radiological terrorism and several have shown promise in pre-clinical testing. In order for these to be developed and useful in clinical radiation therapy applications, it is imperative to demonstrate that they do not protect cancer cells.

The importance of developing agents that sensitize tumor cells, protect or mitigate radiation-induced damage in normal tissue, improve survival, quality of life, and palliative care in cancer patients was emphasized in a recent NCI workshop on *Advanced Radiation Therapeutics - Radiation Injury Mitigation* held on January 25th 2010 (Movsas B, et al. Decreasing the adverse effects of cancer therapy: National Cancer Institute guidance for the clinical development of radiation injury mitigators. Clin Cancer Res. 2011 Jan 15;17(2):222-8. Epub 2010 Nov 3. PMID: 21047979), and in a workshop on *Radiation*

Resistance in Cancer Therapy: Its Molecular Bases and Role of the Microenvironment on its Expression held Sept 1-3, 2010. This contract topic is targeting the clear need of cell-type and tissue-type specific radiomodulators. There is a dearth of radiomodulators available and the projects coming out of this solicitation will drive forward the next generation, and true first generation of radiomodulators. Several SBIR companies have been working in this field and some have partially developed products in response to call for radiation counter-measures (Biomedical Advanced Research Development Authority (BARDA) and National Institute of Allergy and Infectious Diseases (NIAID) funding). The SBIR mechanism is ideal for these businesses to further develop their technology for cancer patients.

Project Goals

This contract topic aims to encourage discovery and development of innovative and promising radioprotectors, mitigators, or sensitizers that either selectively protect normal tissues (but not tumors) against ionizing radiation or selectively sensitize tumors, thereby increasing the therapeutic ratio of radiation. Proposals for radiation modulators are solicited that include preclinical and/or early phase clinical studies demonstrating safety, efficacy, dose, schedule, pharmacokinetics (PK), pharmacodynamics (PD), and metabolism. Proposals should also demonstrate a clear understanding of regulatory requirements, and should include a regulatory plan including key steps such as a pre-IND meeting with FDA, submitting an investigational new drug (IND) application, approval of clinical trial design, and ultimately drug registration.

The goal is to stimulate collaborations among small businesses, academic institutions, and contract research organizations to promote the rapid development of innovative radioresponse modifiers that will decrease normal tissue injury and/or enhance tumor killing, thereby improving radiotherapy outcomes. The long-term goal is to enable small businesses to fully develop, license, and/or market radioresponse modifiers for clinical use.

The contract proposal must describe:

Phase I:

- A quantitative estimate of the patient population that will benefit from the availability of such radioresponse modifiers.
- A plan for generating evidence that the proposed compound(s) protects at least one relevant normal tissue from radiation-induced injury, and/or sensitizes at least two relevant tumor models.
- Either:
    1. A plan for generating evidence that the proposed radioprotector(s)/mitigator(s) does not significantly protect cancer cells, **OR**
    2. A plan for generating evidence that the proposed radiosensitizer(s) does not significantly sensitize normal cells and tissues.
- The plans must include the methodologies proposed to evaluate the preferential effects on normal tissues or tumors by the compound(s) *in vivo* (including appropriate biomarkers and endpoints as determined during early interactions with the FDA).
- Determination of the optimum dose and schedule *in vivo* based upon preclinical pharmacodynamic and pharmacokinetic studies.
- Statistical validation of the proposed study endpoints including where appropriate, power calculations and rationale for proposed sample sizes.

Phase II:

- The approach to early-phase human trials, as indicated, that are designed taking into account the relevant molecular pathways and targets, and aim to gather pharmacodynamic and pharmacokinetic data to confirm the compound's observed behavior in animal studies.

- The approach to assessing the safety and efficacy of the compound(s) in early-phase human trials employing, as appropriate, physician-reported endpoints as well as patient-reported outcomes.

Activities and Expected Deliverables

Phase I may include primarily preclinical studies. Phase II or Fast-Track proposals must contain a section entitled "Regulatory Plan" detailing plans for early involvement of the FDA. There should be a description of how the applicant plans on meeting the requirements to: 1) define suitable biomarkers and endpoints, 2) file IND and 3) design and perform phase 0-2 clinical trials in preparation for product transition to phase 3 clinical trials by groups such as the Radiation Therapy Oncology Group (http://www.rtog.org/).

Where cooperation of other partners is critical for implementation of the proposed methodology, the applicant should provide evidence of such cooperation (through partnering arrangement, letters of support, etc.).

The following deliverables may be required depending on a compound's maturity in the developmental pipeline:

Phase I

- High-throughput screening for rapid identification of active compounds, antibodies or genes which modulate a particular biomolecular pathway or pathways involved in radiation response modification
- Selection and approval of cell panels for *in vitro* testing.
- Demonstration of drug solubility and uptake using cultured normal and transformed cells.
- Study design for determining clonogenic survival or approved alternative tailored to the mechanism of each tested compound.
- Clonogenic survival data or approved alternative validating lack of drug toxicity in normal cells, efficacy and specificity of radioprotection for normal cells and/or efficacy and specificity of radiosensitization for tumor cells.
- Preliminary evidence for lack of *in vivo* toxicity in normal cells or organisms.
- Documentation providing a top-level description of the protocols and the testing results should be provided to NCI as part of the Phase I progress report.

Phase II

For advanced pre-clinical work:

- Design of an NCI/Institutional Animal Care and Use Committee (IACUC)-approved *in vivo* experimentation plan including statistical validation of experimental design/sample size including power calculations.
- In addition, selection and approval of tumor cell panel and normal tissues for *in vitro* testing.
- Demonstration of bioavailability PK and PD in rodent model.
- For radiation protectors / mitigators: demonstration by physiologic testing and histological assessment that irradiated normal tissues are spared over a 6-month period.
- Demonstration of effects (sensitization or lack of protection as appropriate) on tumors using *in vivo* radiation regrowth delay assays.
- Collection of data validating lack of drug toxicity, efficacy, and specificity for normal cells over tumor cells in the case of radiation protectors/mitigators.

Documentation of the testing protocol and testing results should be provided to NCI as part of the Phase II progress report for pre-clinical studies.

For proposals advancing to early phase human trials:

- Identify GMP drug source.
- Obtain IND approval.
- Provide evidence of established clinical collaboration.
- Submitted protocol for IRB approval.
- Define suitable clinical endpoints and patient-oriented outcomes.

Documentation of the testing protocol and testing results should be provided to NCI as part of the Phase I progress report for pre-clinical studies.

Section 12. COMPONENT INSTRUCTIONS AND TECHNICAL TOPIC DESCRIPTIONS, NATIONAL INSTITUTES OF HEALTH, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, Topic 027, is revised and replaced in its entirety as follows:

027 Oral Formulations for Antibiotics of Public Health Importance

Number of anticipated Phase I awards: 4-6

Fast-Track proposals will not be accepted

Budget (total costs): Phase I: $225,000 for up to 1 year; Phase II: $1,500,000 for up to 3 years

Background: Multidrug-resistant pathogens such as tuberculosis (MDR-TB), gonorrhea and staphylococcus are increasingly challenging to treat. Currently existing drugs for the treatment of MDR TB are only moderately potent, show restrictions with absorption or oral bioavailability, and have toxicity profiles that make patient management difficult. There are two important classes of injectable drugs for TB : the aminoglycosides (amikacin and kanamycin) and the polypeptide capreomycin. Capreomycin is recommended for use in cases of known or suspected resistance to the aminoglycosides and seems to have activity against non-replicating persister bacilli, unlike aminoglycosides. However, it is painful to receive by injection and is associated with severe systemic side effects, including nephrotoxicity and ototoxicity. Similarly, treatment of drug-resistant *Neisseria gonorrhea* is an escalating public health concern due to the unavailability of oral dosage forms of antibiotics that are efficacious for this infection. Effective treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) is also challenging to manage because it requires long-term intravenous administration of vancomycin. Oral formulations of licensed antibiotics to treat these and other bacterial pathogens of public health importance are wanted, particularly to address to the growing incidence of drug resistant infections.

Project goal: The goal of this solicitation is to develop an effective oral dosing formulation or modification of licensed antibiotics that are currently only available as intravenously or parenterally-administered formulations, specifically, capreomycin, meropenem, imepenem or vancomycin. Considerations for formulation may also include mitigation of adverse drug reactions. An example is the formulation of capreomycin for oral administration that maintains efficacy while possibly decreasing adverse events (nephrotoxicity and ototoxicity), for use as part of a drug regimen for the treatment of MDR-TB. A second example is an oral formulation of vancomycin that allows for systemic absorption in order to treat MRSA.

Phase I activities:

• Development of methodologies to be used to formulate capreomycin, meropenem, imepenem or vancomycin for oral administration

- Development and implementation of a plan for a biological testing component to quantitatively assess the product(s) for:
    - In vitro activity in an existing standardized, reproducible, and validated in vitro culture and intracellular test systems, and provide quantitative assessment of efficacy and cytotoxicity of the formulated products(s) and/or
    - In vivo efficacy in an existing standardized, reproducible, and validated small animal model of infection which detects statistically valid differences between formulated and non-formulated products for drug efficacy, toxicity and pharmacokinetics

Phase II activities

- Extended preclinical studies
- Development of a well-defined formulation under good manufacturing practices (GMP)
- Uniformity from lot –to-lot and to be certified under quality control
- Scale-up and production for future Phase I clinical study

-END OF AMENDMENT-